The statistics of cancer survival - What are the true survival benefits associated with new cancer treatments?

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- Health Economics
- What is treatment crossover and why does it occur?
- What problems are created by treatment crossover?
- How important is treatment crossover?
- What are the potential solutions?
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Health Economics

- Appraise new treatments to see if they are “cost-effective”

➔Should the NHS buy them?

- NHS has a fixed budget – has to try to maximise health benefits by buying the most cost-effective treatments

➔Need a generic outcome measure – the QALY

➔And a cost-effectiveness threshold

- Need to estimate costs and QALYs accurately so that consistent decisions can be made

➔For cancer treatments, survival is likely to be key

Treatment crossover (1)

- In RCTs often patients are allowed to switch from the control treatment to the new intervention after a certain timepoint (eg disease progression)

➔ PFS (progression free survival) estimates are ok

➔ But OS (overall survival) estimates will be confounded

- What are the implications of this?
  - For clinical analysis
  - For economic analysis

  ➔ There are different drivers for these two analyses

Treatment crossover (2)

- **Clinical analysis**
  - Drug regulatory bodies such as FDA and EMA accept that PFS is sufficient for licensing
  - There are reduced incentives for companies to collect longer term survival data
  - There are reduced incentives to maintain randomisation post-progression

  ➔Practical reason why treatment crossover occurs

  ➔Combined with ethical reasons, strong incentives to allow crossover

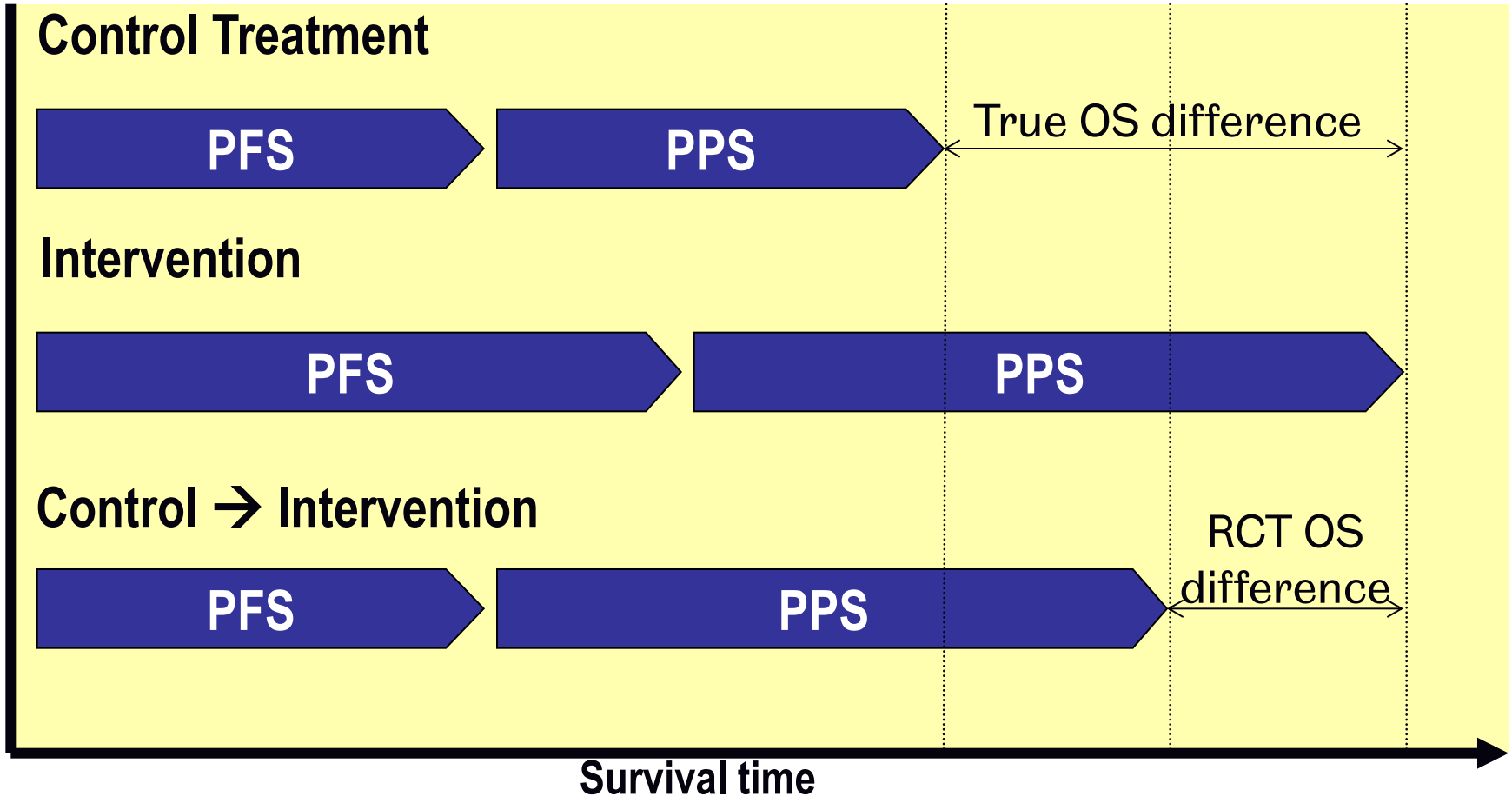
- **Economic analysis**
  - For interventions that impact upon survival OS is a key input in the economic model
  - Need accurate estimates of the treatment effect on PFS *and* OS

Treatment crossover (3)

- Treatment crossover is ***not*** just an issue for economic evaluation
- But it can appear that way because it becomes more of an issue at the "fourth hurdle"
- **Implications:**
  - Cost effectiveness results will be inaccurate → an ITT analysis is likely to underestimate the treatment benefit

➔**Inconsistent and inappropriate treatment recommendations could be made**

Treatment crossover (4)



Crossover is likely to result in an underestimate of the treatment effect

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What is usually done to adjust?

- No clear consensus
- Numerous 'naive' approaches have been taken in [illegible]:
  - Take no action at all
  - Exclude or censor all patients who crossover

Very prone to selection bias – crossover isn't random

- Occasionally more complex statistical methods have been used, eg:
  - Rank Preserving Structural Failure Time Models (RPSFTM)
  - Inverse Probability of Censoring Weights (IPCW)
- And others are available from the literature, eg:
  - Structural Nested Models (SNM)

What are the consequences?

NICE TA 215, Pazopanib for RCC [51% of control switched]

- ITT: OS HR (vs IFN) = *1.26* → *ICER = Dominated*
- Censor patients: HR = *0.80* → *ICER = £71,648*
- Exclude patients: HR = *0.48* → *ICER = £26,293*
- IPCW: HR = *0.80* → *ICER = £72,274*
- RPSFTM: HR = *0.63* → *ICER = £38,925*

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Potential solutions (1)

RPSFTM

- Developed for use on RCT datasets, makes use of randomisation to estimate counterfactual survival times

Key assumption: common treatment effect

IPCW

- Developed for use on observational datasets, censors xo patients, weights remaining patients, runs weighted Cox model

Key assumptions: "no unmeasured confounders"; must model OS *and* crossover using covariate data

SNM

- Observational version of RPSFTM

Key assumptions: "no unmeasured confounders"; must model OS *and* crossover

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Potential solutions (2)

Another option…

- Consider the treatment crossover typically seen in oncology trials…
- Data on PFS is required for licensing, thus only allow crossover post-progression
- ***If*** crossover only happens after progression, and happens soon after progression, we may consider a simple "two-stage" approach:
  - Use disease progression as a secondary baseline for control group patients and consider control group data after this time-point as an observational dataset
  - Apply an accelerated failure time model to this dataset including covariates for crossover and other prognostic covariates measured at the secondary baseline
  - Use the AF derived for crossover to "shrink" survival times of switchers

  ➔ Counterfactual dataset

Key assumptions: "no unmeasured confounders" at secondary baseline time-point; crossover only after progression, and soon after progression

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Simulation study (1)

- None of these methods are perfect
- But we need to know which are likely to produce least bias in different scenarios

➔**Simulation study**

- Simulate survival data for two treatment groups, applying crossover that is linked to patient characteristics/prognosis
- In some scenarios simulate a treatment effect that changes over time
- In some scenarios simulate a treatment effect that remains constant over time
- Test different %s of crossover, and different treatment effect sizes

➔***How does the bias and coverage associated with each method compare?***

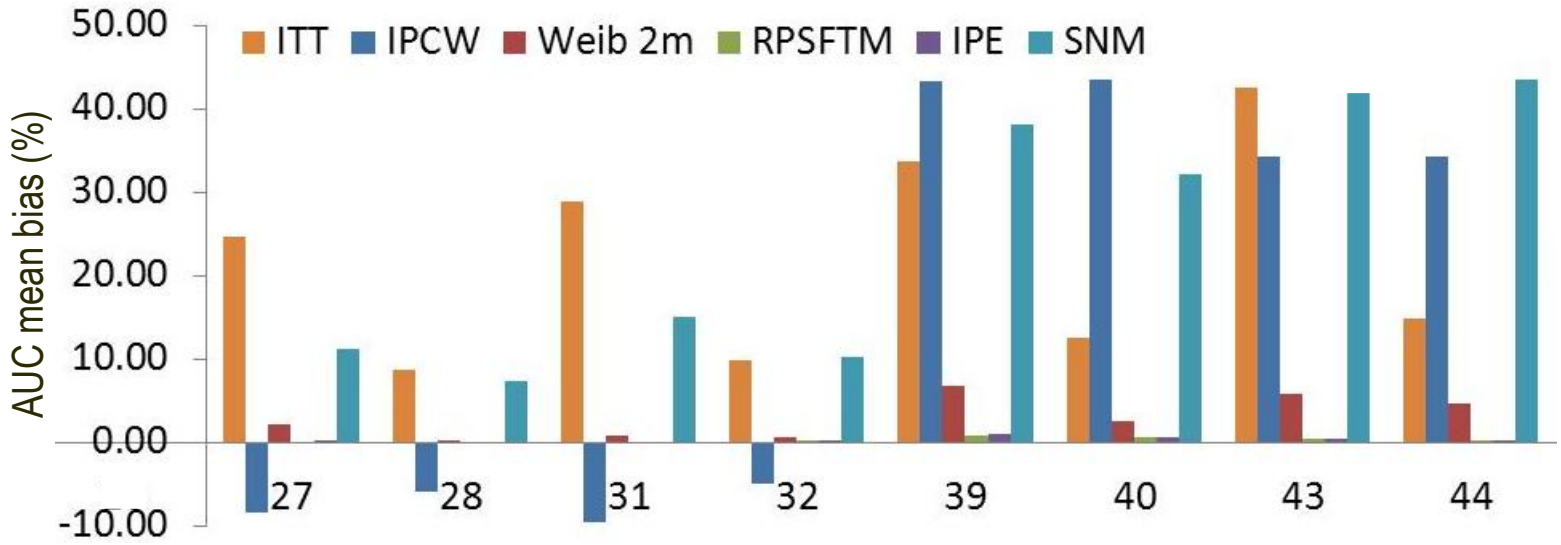
Simulation study (2)

Methods assessed

- **Naive methods**
  - ITT
  - Exclude crossover patients (PPexc)
  - Censor crossover patients (PPcens)
  - Treatment as a time-dependent covariate (TDCM)
- **Complex methods**
  - RPSFTM
  - IPE algorithm
  - IPCW
  - SNM
  - Two-stage Weibull

Results: common effect

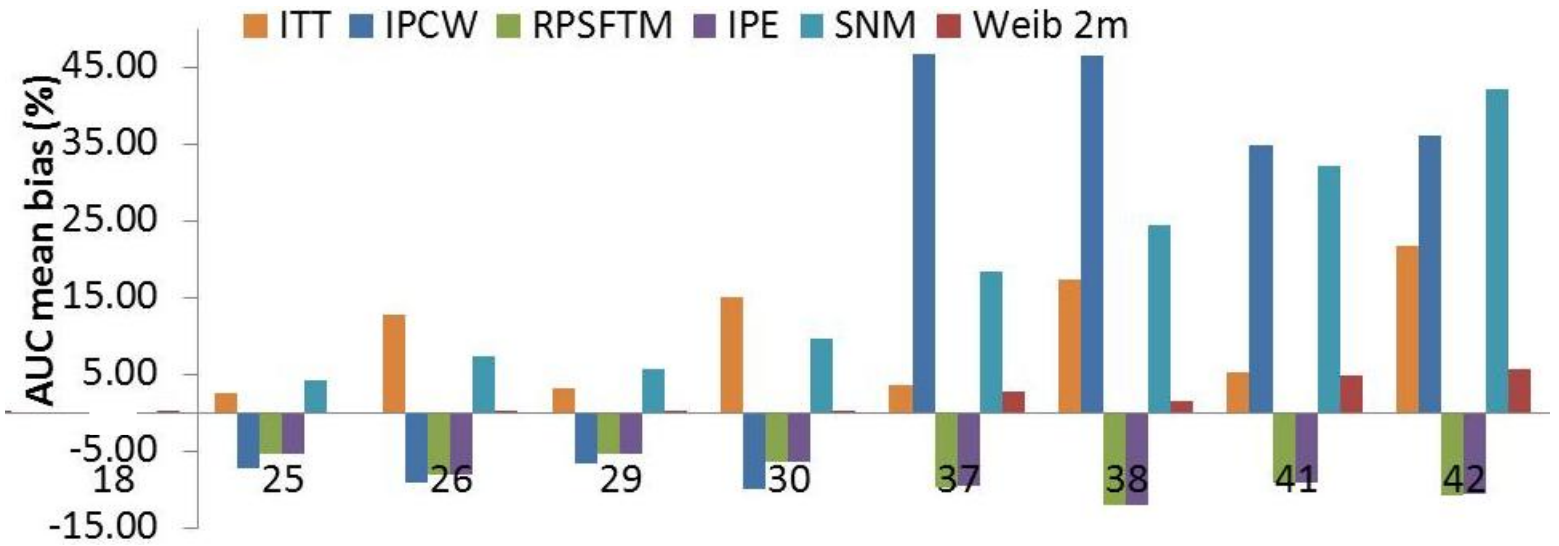
- RPSFTM / IPE worked very well
- IPCW and SNM performed ok when crossover % was lower



- IPCW and SNM performed poorly when crossover % was very high
- Naive methods performed poorly (generally led to higher bias than ITT)
- Two-stage Weibull performed well

Results: effect 15% ↓ in xo patients

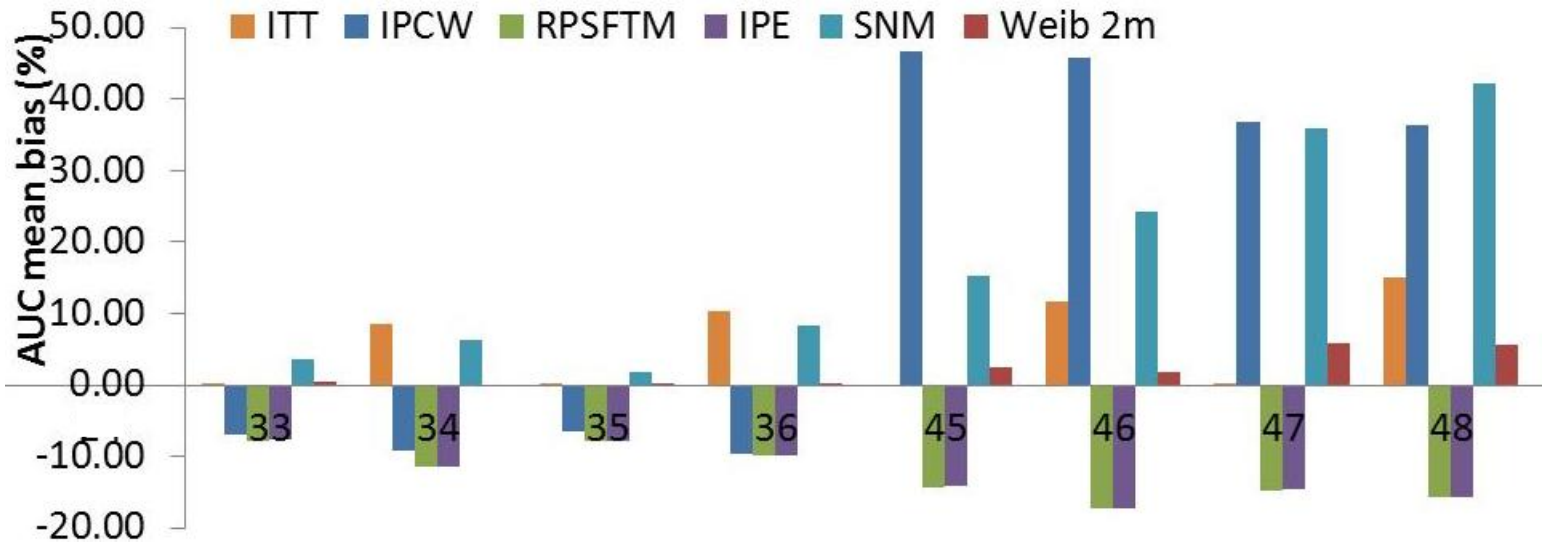
- RPSFTM / IPE produced higher bias than previous scenarios
- IPCW and SNM performed similarly to RPSFTM / IPE providing crossover < 90%



- IPCW and SNM performed poorly when crossover % was very high
- Bias not always lower than that associated with the ITT analysis
- Two-stage Weibull performed well

Results: effect 25% ↓ in xo patients

- RPSFTM / IPE produce substantial bias
- IPCW and SNM produce less bias than RPSFTM / IPE providing crossover < 90%



- Few 'good' options when crossover % is very high
- Often ITT analysis likely to result in least bias (esp. when trt effect low)
- But two-stage Weibull still does quite well

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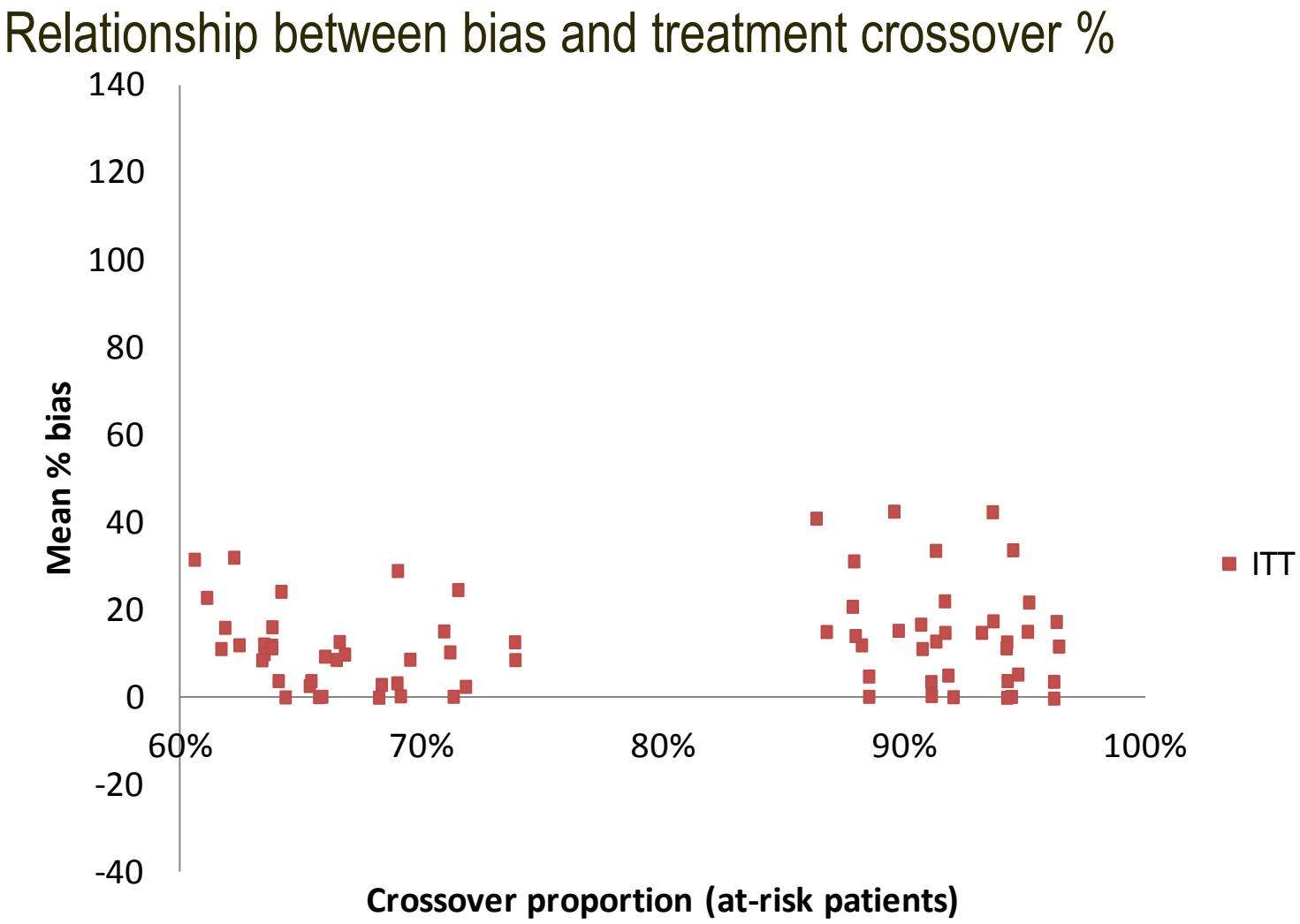
Results cont.



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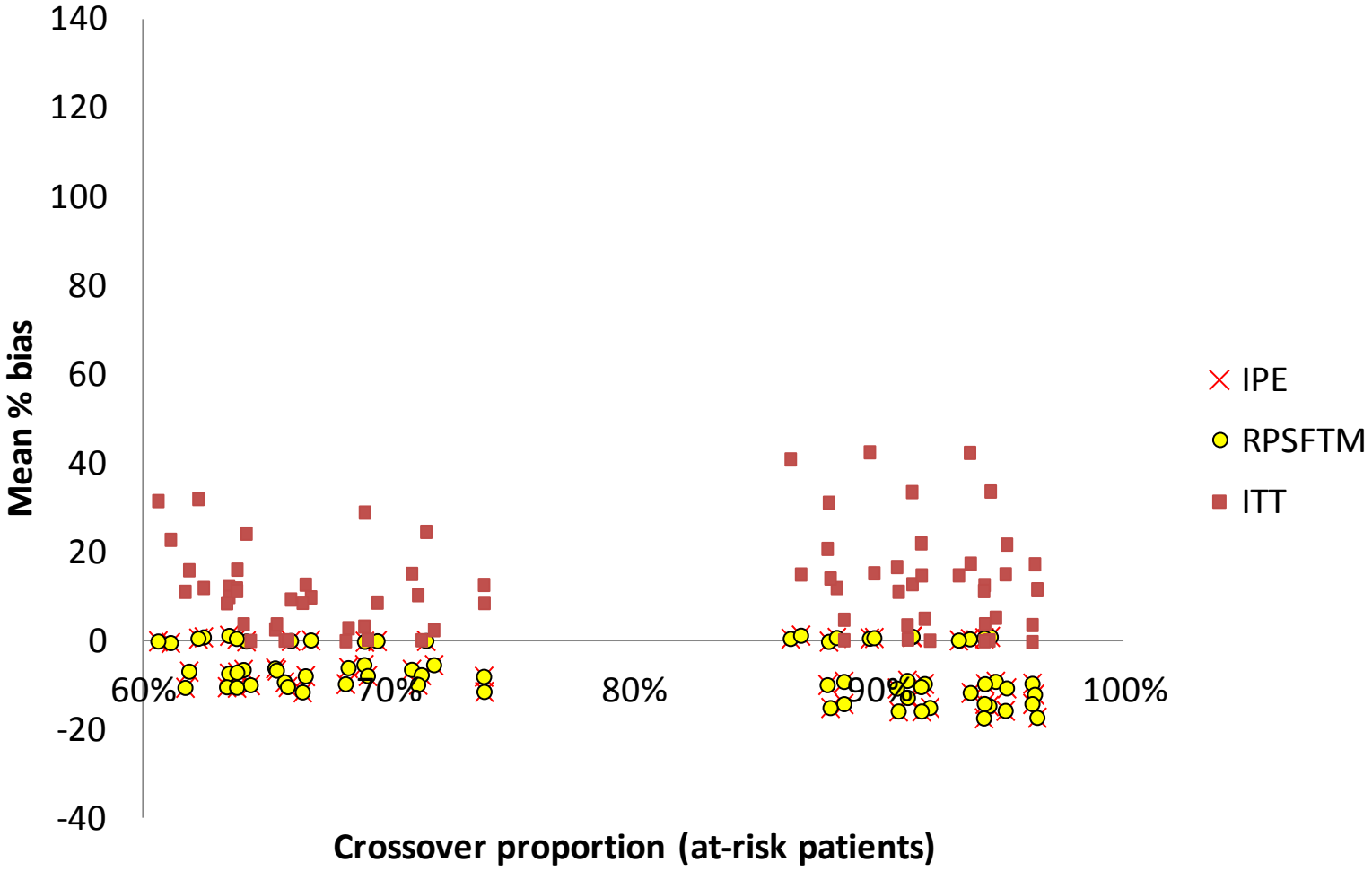
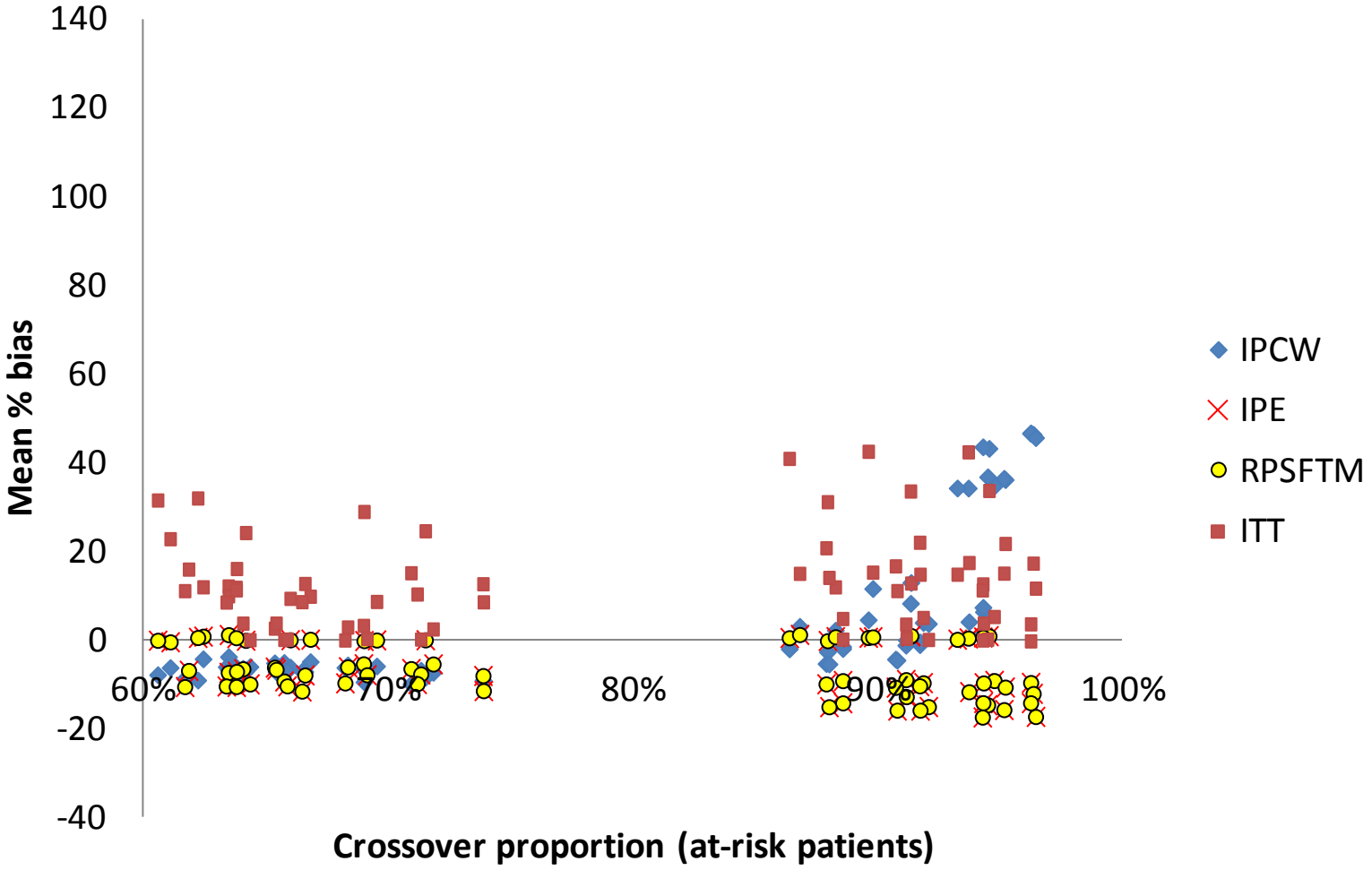
Results cont.

Relationship between bias and treatment crossover %



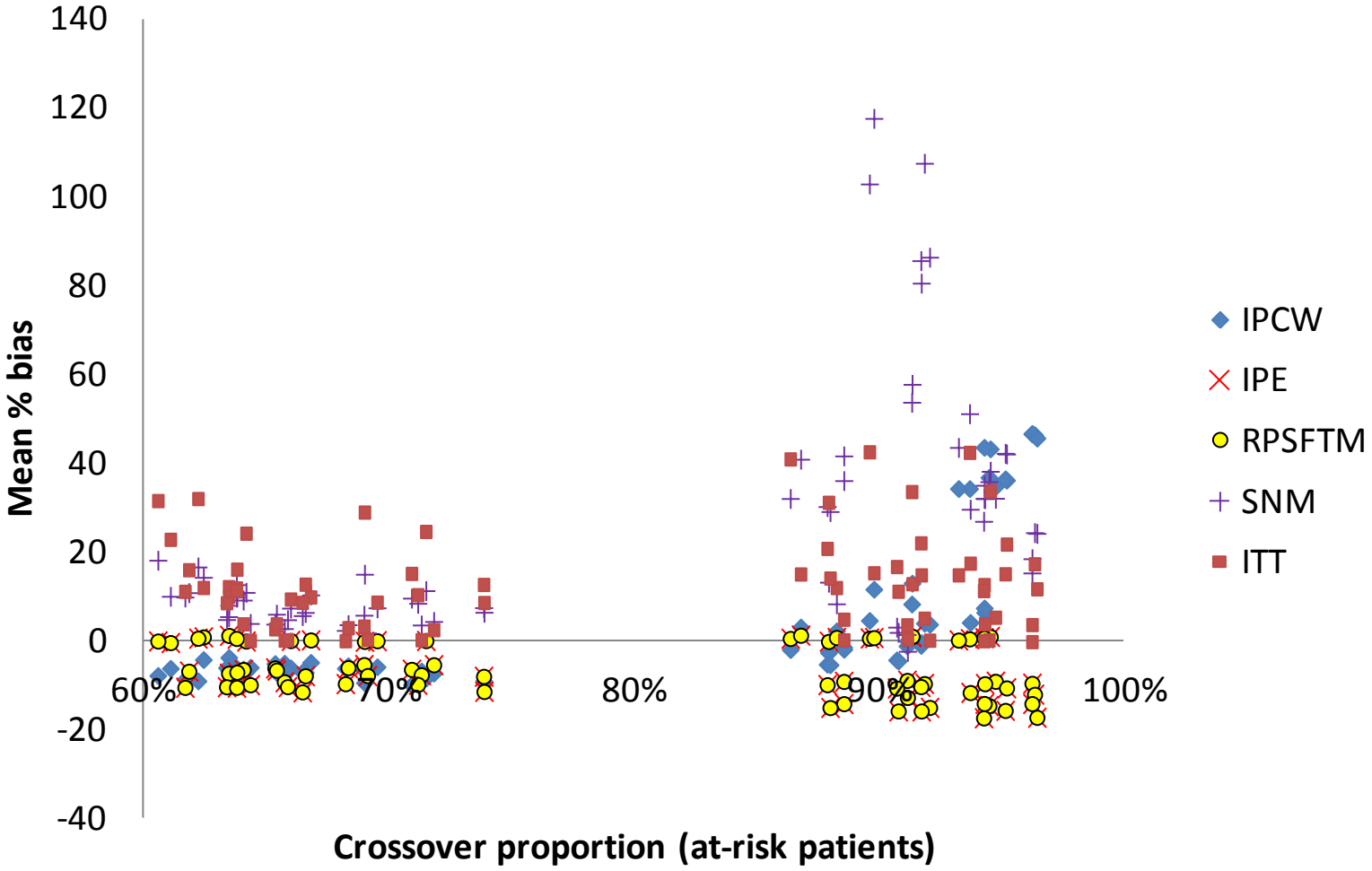
Results cont.

Relationship between bias and treatment crossover %



Results cont.

Relationship between bias and treatment crossover %



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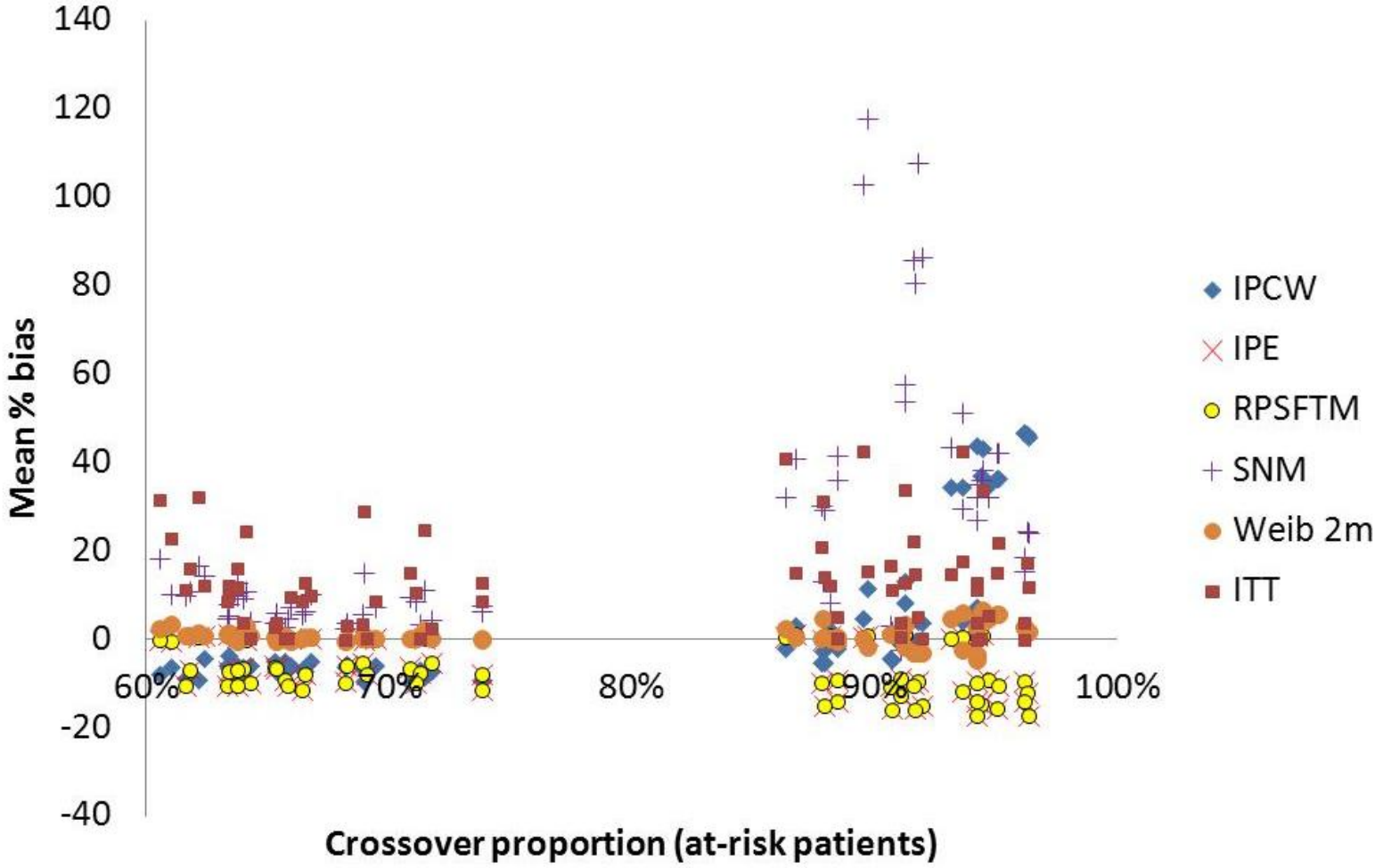
Results cont.

Relationship between bias and treatment crossover %



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How can we select the most appropriate method?

- Even the more complex methods have important limitations and will often result in bias in realistic scenarios
- "Naive" methods should not be used

1. What was the crossover mechanism? Who, when, why and how many?
2. What is the nature of the treatment effect?
3. What / how much data are available? Important time-dependent cova

What about patient preferences?

- Each of these questions helps determine whether ITT, RPSFTM, IPE, IPCW or two-stage methods are likely to be suitable
- How plausible are their assumptions in an oncology RCT context?

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Limitations

- Other scenarios would be interesting
  - Lower crossover proportions
  - Different sample sizes
  - Different treatment effect decrements
- Data generating model
  - We used a joint longitudinal and survival model starting off with a Weibull distribution
  - Does this influence the results?
- New methods are required!

Conclusions (1)

- Treatment crossover is an important issue that has come to the fore in HE arena
- Current methods for dealing with treatment crossover are imperfect and have been used uncertainly in HTA
- Our study offers evidence on bias in different scenarios (subject to limitations)

Conclusions (2)

- RPSFTM / IPE produce low bias when treatment effect is common
  → But are very sensitive to this
- IPCW / SNM are not affected by changes in treatment effect between groups, but in (relatively) small trial datasets observational methods are volatile
  → Especially when crossover % is very high (leaving low *n* in control group)
- Simple two-stage methods are worthy of consideration
- Very important to assess trial data, crossover mechanism, treatment effect to determine which method likely to be most appropriate
- There is a definite requirement for clinical opinion, to determine justifiable methods

→ **Don't just pick one!!**